

**Translation**

**PATENT COOPERATION TREATY**

**PCT**

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**  
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>P03-0116PCT</b>	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. <b>PCT/JP2004/012422</b>	International filing date (day/month/year) <b>23.08.2004</b>	Priority date (day/month/year) <b>21.08.2003</b>
International Patent Classification (IPC) or national classification and IPC <b>A61K45/00, 31/335, 31/343, 31/7072, 31/7105, 48/00, A61P9/02, 29/00, 37/06</b>		
Applicant <b>Locomogene, Inc.</b>		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of <u>8</u> sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising: a. <input type="checkbox"/> (sent to the applicant and to the International Bureau) a total of _____ sheets, as follows: <input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). <input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. <input checked="" type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) <u>1</u> , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items: <input checked="" type="checkbox"/> Box No. I Basis of the report <input type="checkbox"/> Box No. II Priority <input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability <input type="checkbox"/> Box No. IV Lack of unity of invention <input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement <input type="checkbox"/> Box No. VI Certain documents cited <input type="checkbox"/> Box No. VII Certain defects in the international application <input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/JP	Authorized officer
Facsimile No.	Telephone No.

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

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Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following \_\_\_\_\_, which is the language of a translation furnished for the purposes of:
- ☐ international search (Rule 12.3 and 23.1(b))
- ☐ publication of the international application (Rule 12.4)
- ☐ international preliminary examination (Rule 55.2 and/or 55.3)
2. With regard to the elements of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):
- ☒ the international application as originally filed/furnished
- ☐ the description:
- pages \_\_\_\_\_ as originally filed/furnished
- pages\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- pages\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- ☐ the claims:
- nos. \_\_\_\_\_ as originally filed/furnished
- nos.\* \_\_\_\_\_ as amended (together with any statement) under Article 19
- nos.\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- nos.\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- ☐ the drawings:
- sheets \_\_\_\_\_ as originally filed/furnished
- sheets\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- sheets\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- ☒ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages \_\_\_\_\_
- ☐ the claims, nos. \_\_\_\_\_
- ☐ the drawings, sheets/figs \_\_\_\_\_
- ☐ the sequence listing (*specify*): \_\_\_\_\_
- ☐ any table(s) related to sequence listing (*specify*): \_\_\_\_\_
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages \_\_\_\_\_
- ☐ the claims, nos. \_\_\_\_\_
- ☐ the drawings, sheets/figs \_\_\_\_\_
- ☐ the sequence listing (*specify*): \_\_\_\_\_
- ☐ any table(s) related to sequence listing (*specify*): \_\_\_\_\_

\* If item 4 applies, some or all of those sheets may be marked "superseded."

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application☒ claims Nos. 8, 9

because:

☒ the said international application, or the said claims Nos. 8, 9  
relate to the following subject matter which does not require an international preliminary examination (*specify*):

The subject matter of claims 8 and 9 includes  
methods of treatment of the human body by therapy.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. \_\_\_\_\_  
are so unclear that no meaningful opinion could be formed (*specify*):☐ the claims, or said claims Nos. \_\_\_\_\_ are so inadequately supported  
by the description that no meaningful opinion could be formed.☒ no international search report has been established for said claims Nos. 8, 9☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished☐ does not comply with the standard

the computer readable form

☐ has not been furnished☐ does not comply with the standard☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.☐ See Supplemental Box for further details.

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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**Box No. V** Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

## 1. Statement

Novelty (N)	Claims	<u>3-7</u>	YES
	Claims	<u>1, 2</u>	NO
Inventive step (IS)	Claims		YES
	Claims	<u>1-7</u>	NO
Industrial applicability (IA)	Claims	<u>1-7</u>	YES
	Claims		NO

## 2. Citations and explanations (Rule 70.7)

Documents cited in the international search report:

Document 1: Yasukazu Katayama et al., Experimental Medicine, 2001, Vol. 19, No. 13, pages 1695 to 1702

Document 2: Hiroyuki Hagiya et al., Igaku no Ayumi, 7 June 2003, Vol. 205, No. 10: pages 763 to 767

Document 3: WO 02/052007 A1

Document 4: Kaneko M. et al., FEBS Lett. 4 December 2002, Vol. 532 (1-2), pages 147 to 152

Claims 1 and 2

The invention set forth in claims 1 and 2 lacks novelty and does not involve an inventive step in the light of document 1.

As set forth in document 1, it would be known to a person skilled in the art at the time of filing of this application that tunicamycin, tapsigargin and brefeldin A are substances which are capable of inducing endoplasmic reticulum stress (see Table 1), and that excessive endoplasmic reticulum stress causes apoptosis (see page 1698, left column, line 11 to right column, line 9; fig. 3).

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Box No. V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;  
citations and explanations supporting such statementClaim 3

The invention set forth in claim 3 does not involve an inventive step in the light of documents 1 and 4.

Document 4 indicates that endoplasmic reticulum stress-induced apoptosis is suppressed by HRD1 (corresponding to "synoviolin" in this application), and it would be easy for a person skilled in the art to attempt to induce apoptosis by suppressing the function of HRD1 by using siRNA or the like. Moreover, a person skilled in the art would be capable of combining said substance with another apoptosis-inducing agent.

Claims 4 to 6

The invention set forth in claims 4 to 6 does not involve an inventive step in the light of documents 1 and 2.

Document 2 suggests that the existence of apoptosis-inhibiting factors and the existence of an apoptosis resistance mechanism is involved with the abnormal proliferation of periosteum, and suggests that it may be possible to treat articular rheumatism by inducing apoptosis. It would therefore be easy for a person skilled in the art to attempt to use a compound with an apoptosis-inducing activity, such as that set forth in document 1, in the treatment of articular rheumatism.

Claim 7

The invention set forth in claim 7 does not involve an inventive step in the light of documents 1 to 3.

Document 3 indicates that synoviolin is strongly expressed in periosteal tissue of patients with rheumatism, and that periosteal cells proliferate in

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;  
citations and explanations supporting such statement

response to synoviolin (see page 30, lines 8 to 11). It would therefore be easy for a person skilled in the art to attempt to treat articular rheumatism by suppressing the periosteal cell proliferation activity of synoviolin using siRNA or the like. Moreover, a person skilled in the art would be capable of combining said substance with another articular rheumatism treatment agent as necessary.

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## Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

(1) The "substance capable of inducing endoplasmic reticulum stress" set forth in claims 1, 3, 4, 6 and 7 covers all compounds having such a property. However, it appears that only some of the claimed compounds (in particular, tunicamycin, tapsigargin and brefeldin A set forth in claims 2 and 5) are disclosed within the meaning of PCT Article 5, and hence this subject matter is not fully supported by the description within the meaning of PCT Article 6.

(2) The "therapeutic agent for autoimmune disease" set forth in claims 4, 5 and 7 covers all types of therapeutic agents for autoimmune diseases. However, only the agent for articular rheumatism set forth in claim 6 is concretely disclosed within the meaning of PCT Article 5. Taking into account the fact that the disclosure of the description of this application relates particularly to inhibition of the proliferation of synovial cells, it appears that the invention is not fully supported by the description within the meaning of PCT Article 6 with respect to the treatment of other autoimmune diseases.

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## Supplemental Box Relating to Sequence Listing

## Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:
- a. type of material
- ☒ a sequence listing
- ☐ table(s) related to the sequence listing
- b. format of material
- ☐ in written format
- ☒ in computer readable form
- c. time of filing/furnishing
- ☐ contained in the international application as filed
- ☒ filed together with the international application in computer readable form
- ☐ furnished subsequently to this Authority for the purposes of search and/or examination
- ☐ received by this Authority as an amendment\* on \_\_\_\_\_
2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

\* If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."